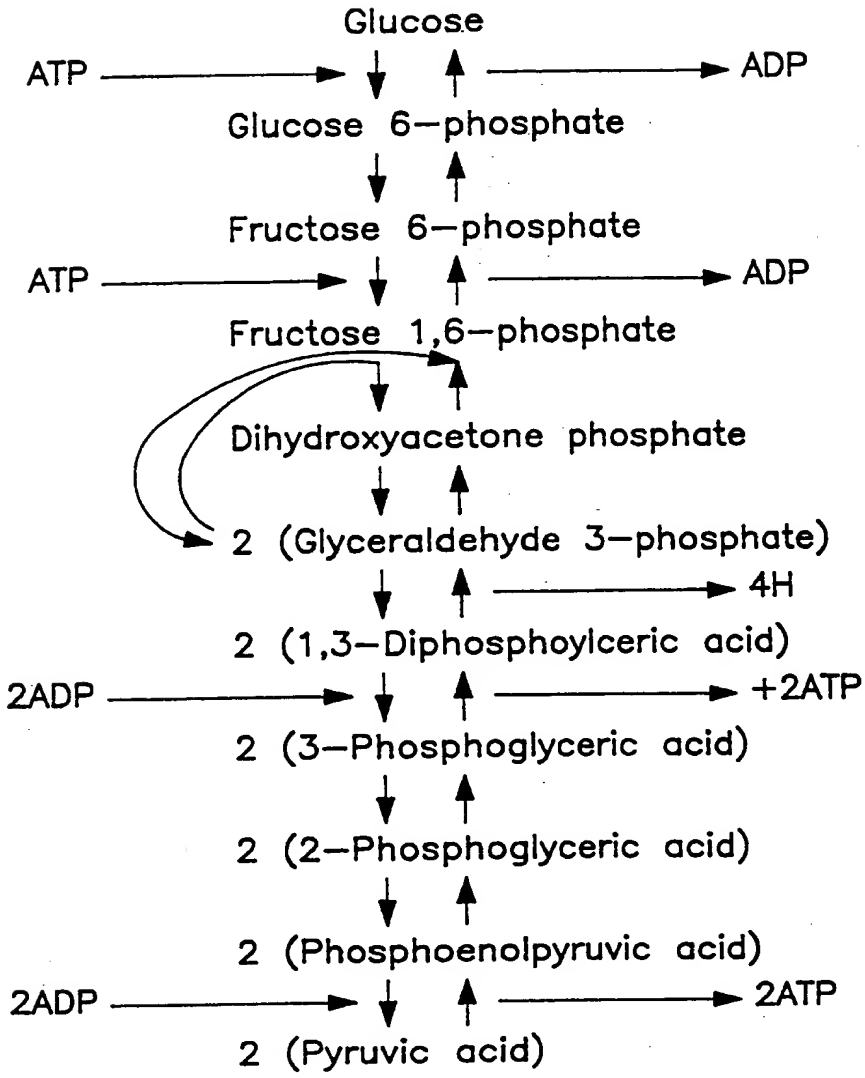
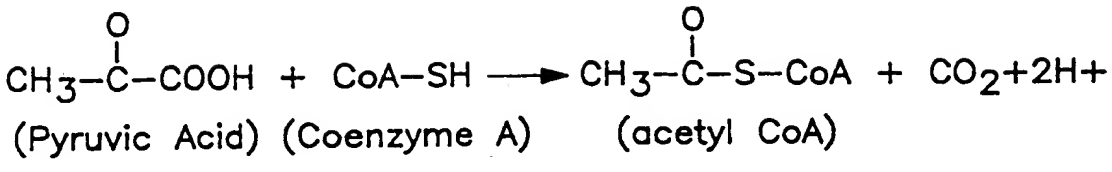



NET REACTION PER MOLECULE OF GLUCOSE:
Glucose+2ADP+2$PO_4^{---}$ → 2 Pyruvic acid+2ATP+4H+HEAT

FIG. 1


CH3–C–COOH + CoA–SH → CH3–C–S–CoA + CO2+2H+
(Pyruvic Acid) (Coenzyme A) (acetyl CoA)

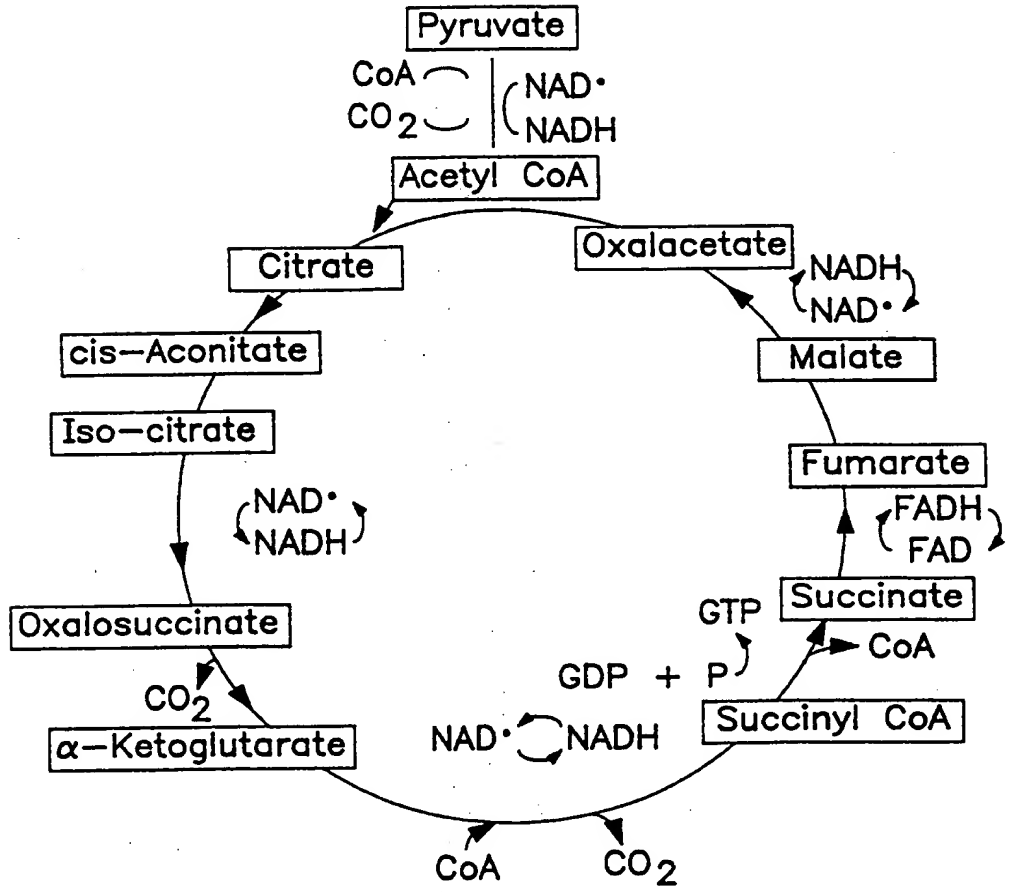

Pyruvate
CoA
CO2
NAD•
NADH
Acetyl CoA
Citrate
Oxalacetate
NADH
NAD•
cis–Aconitate
Malate
Iso–citrate
Fumarate
NAD•
NADH
FADH
FAD
Oxalosuccinate
GTP
Succinate
CoA
GDP + P
CO2
Succinyl CoA
α–Ketoglutarate
NAD•
NADH
CoA
CO2

FIG. 2

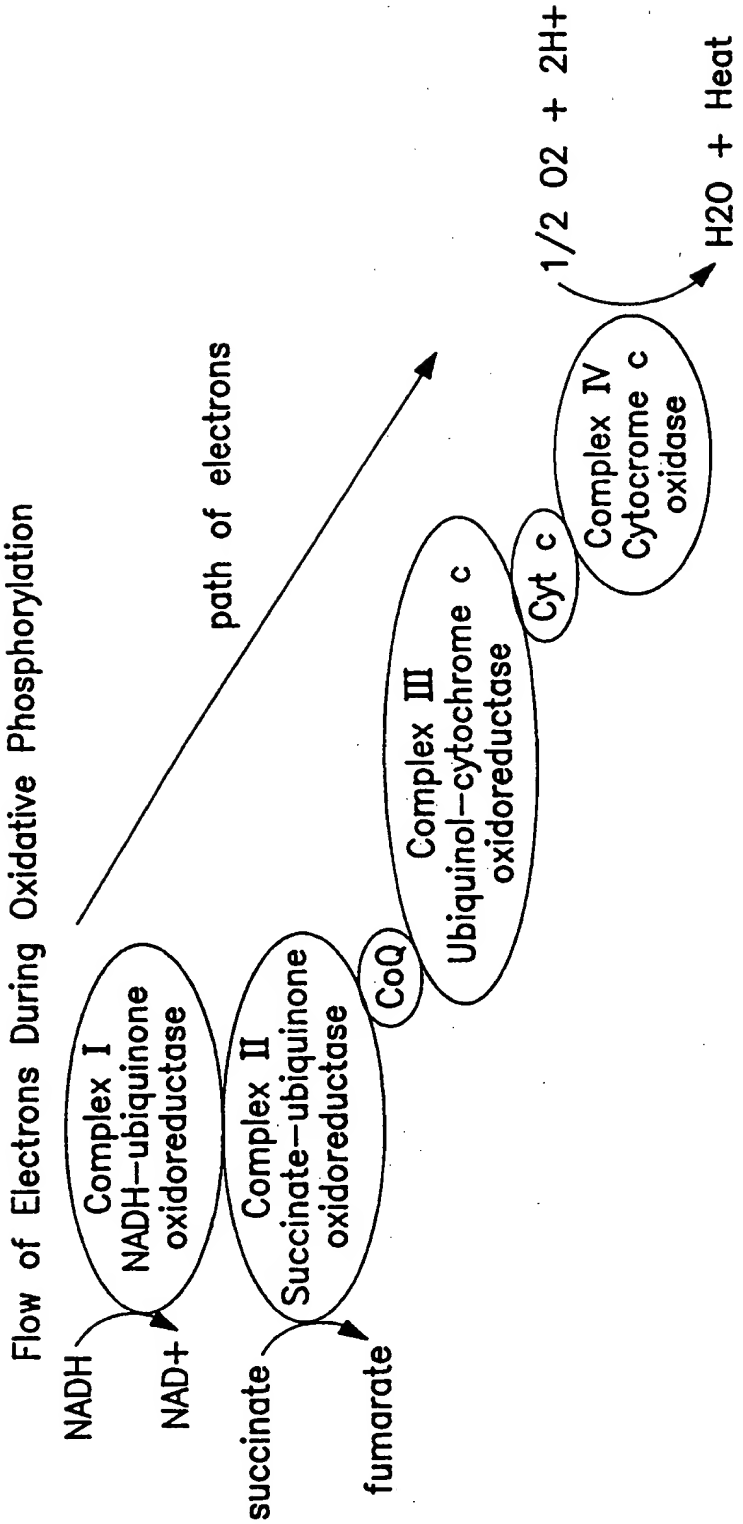

Flow of Electrons During Oxidative Phosphorylation
path of electrons
Complex I
NADH–ubiquinone
oxidoreductase
Complex II
Succinate–ubiquinone
oxidoreductase
CoQ
Complex III
Ubiquinol–cytochrome c
oxidoreductase
Cyt c
Complex IV
Cytocrome c
oxidase
NADH
NAD+
succinate
fumarate
1/2 O2 + 2H+
H2O + Heat

FIG. 3

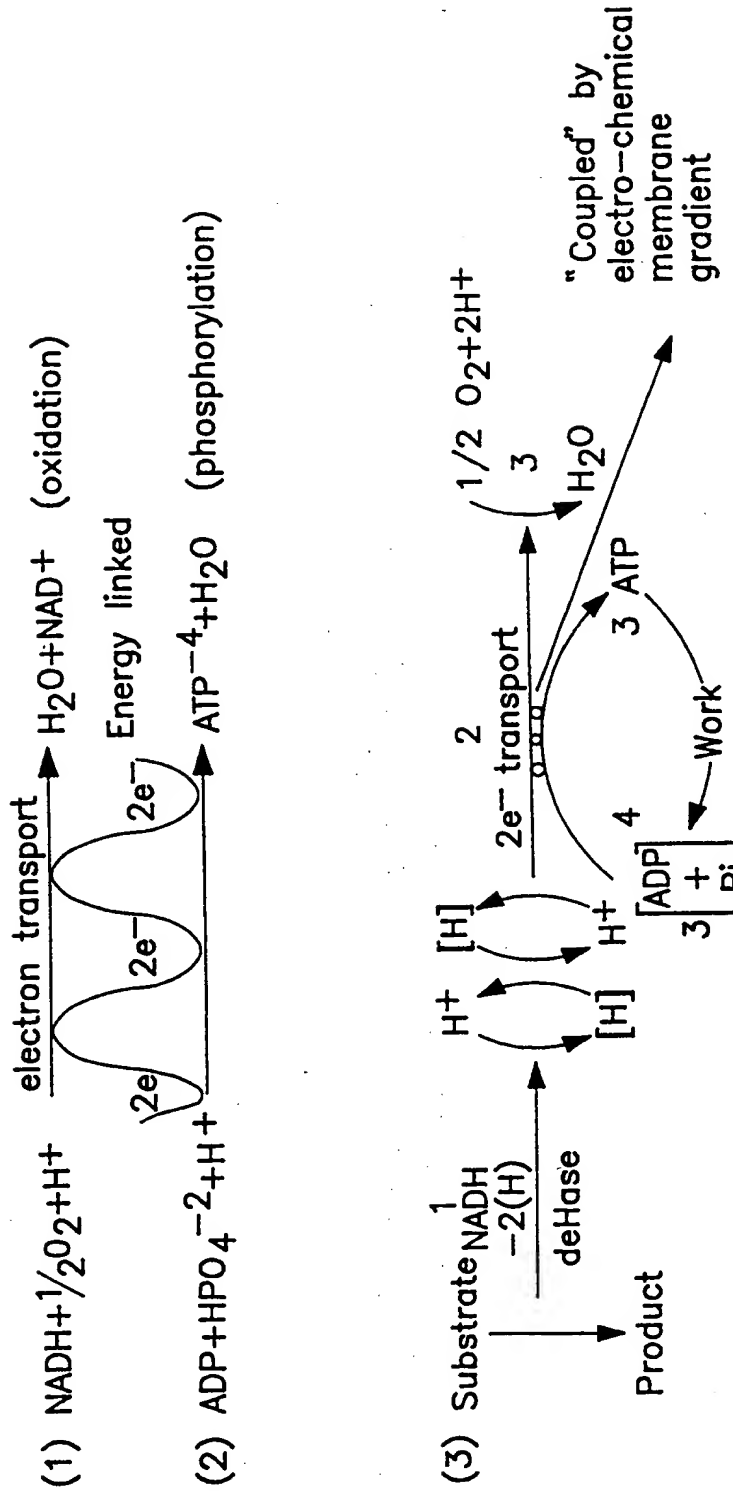

(1) NADH+1/2O2+H+
electron transport
H2O+NAD+ (oxidation)
Energy linked
2e
2e
2e
(2) ADP+HPO4−2+H+
ATP−4+H2O (phosphorylation)
(3) Substrate
1
NADH
−2(H)
deHase
Product
H+ [H]
[H] H+
2
2e− transport
1/2 O2+2H+
3
H2O
"Coupled" by electro-chemical membrane gradient
3 ATP
4
3 [ADP + Pi]
Work

FIG. 4

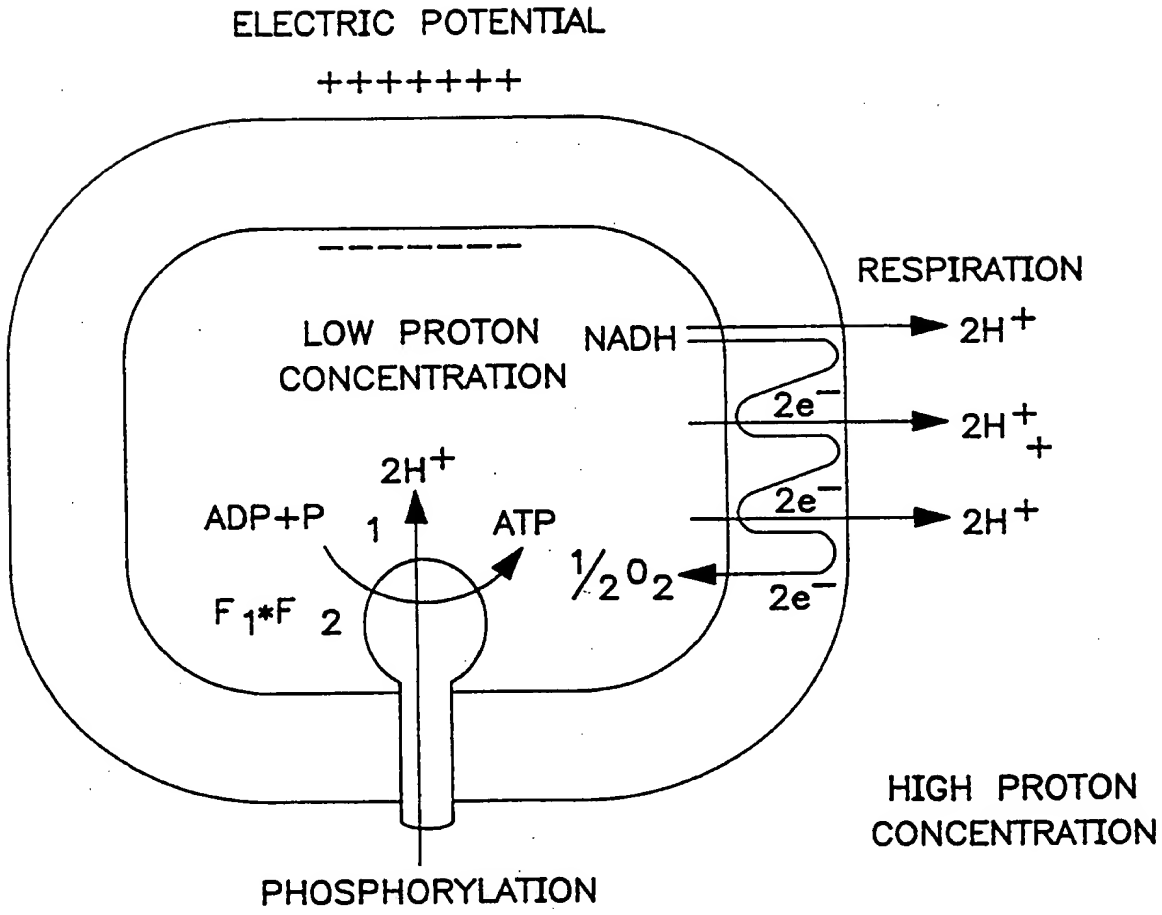

ELECTRIC POTENTIAL
+++++++
-------
RESPIRATION
LOW PROTON CONCENTRATION
NADH
2H+
2e−
2H+
2e−
2H+
2H+
ADP+P
1
ATP
½ O2
2e−
F1*F2
HIGH PROTON CONCENTRATION
PHOSPHORYLATION

FIG. 5

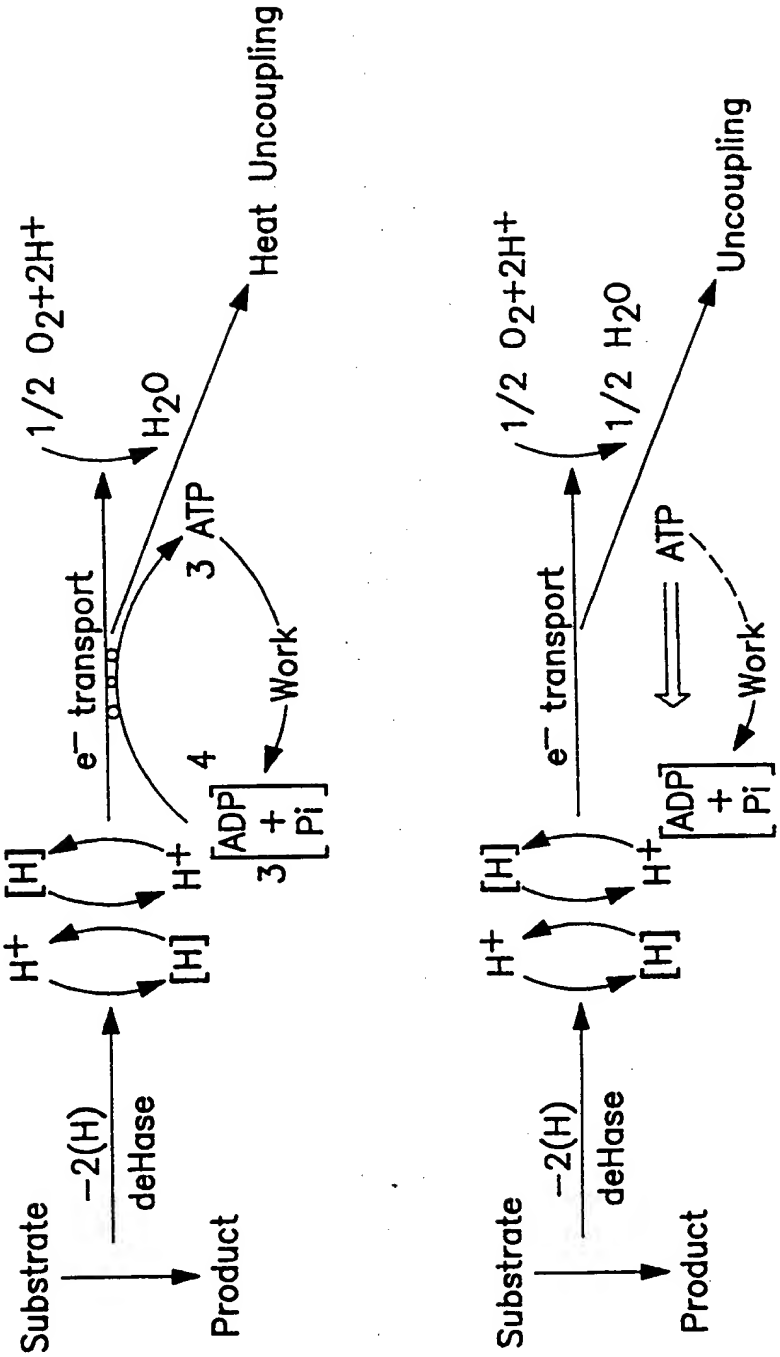
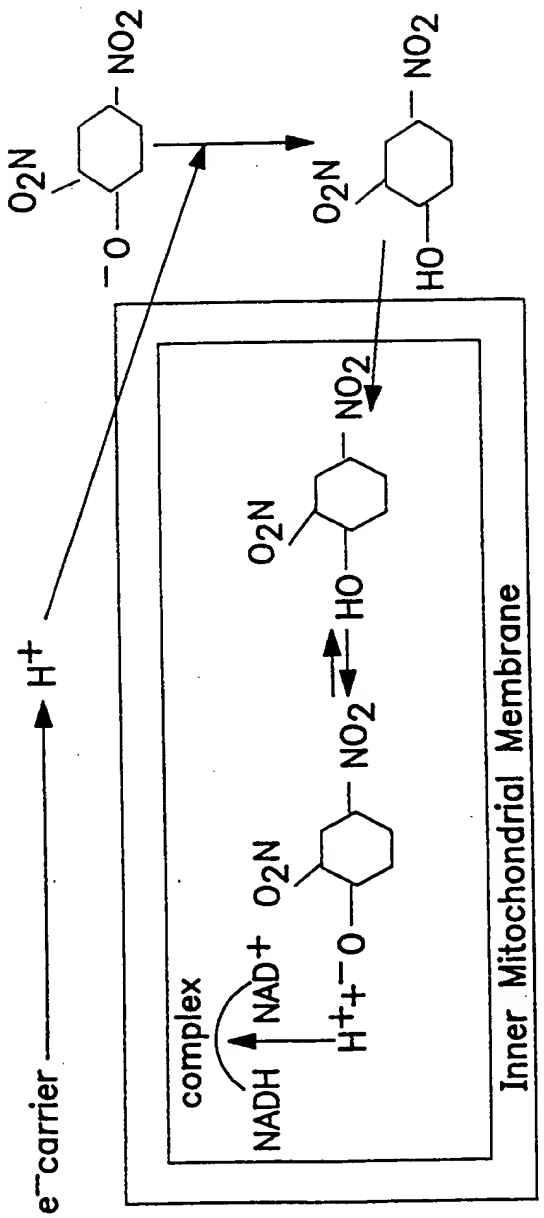

Substrate
−2(H)
deHase
Product
H+
[H]
H+
[H]
e− transport
1/2 O2+2H+
H2O
Heat Uncoupling
3 ATP
Work
4
3 [ADP + Pi]
Substrate
−2(H)
deHase
Product
H+
[H]
H+
[H]
e− transport
1/2 O2+2H+
1/2 H2O
Uncoupling
ATP
Work
[ADP + Pi]

FIG. 6


$O_2N$
$NO_2$
$-O$
HO
$H^+$
$e^-$carrier
NADH
$NAD^+$
complex
Inner Mitochondrial Membrane

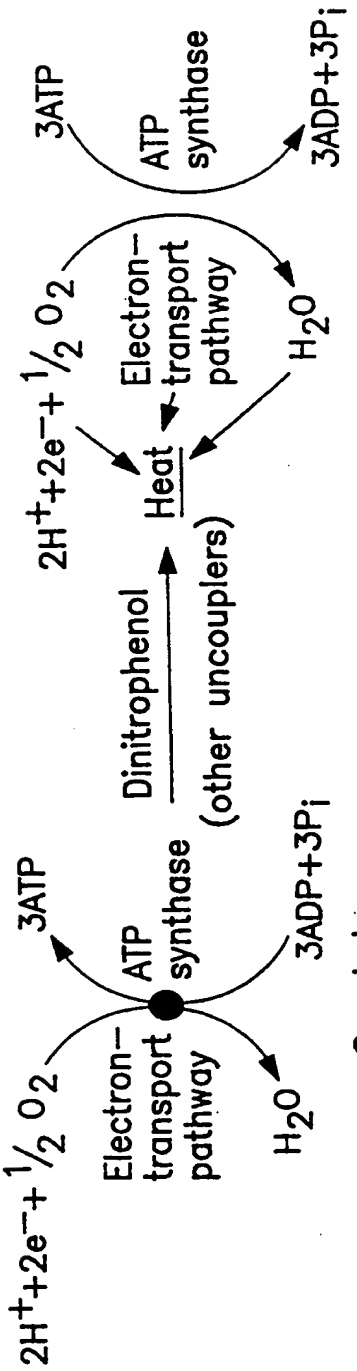

3ATP
ATP synthase
3ADP+3Pi
Uncoupled
$2H^+ + 2e^- + \frac{1}{2} O_2$
Electron-transport pathway
$H_2O$
Heat
Dinitrophenol
(other uncouplers)
Coupled

FIG. 6a

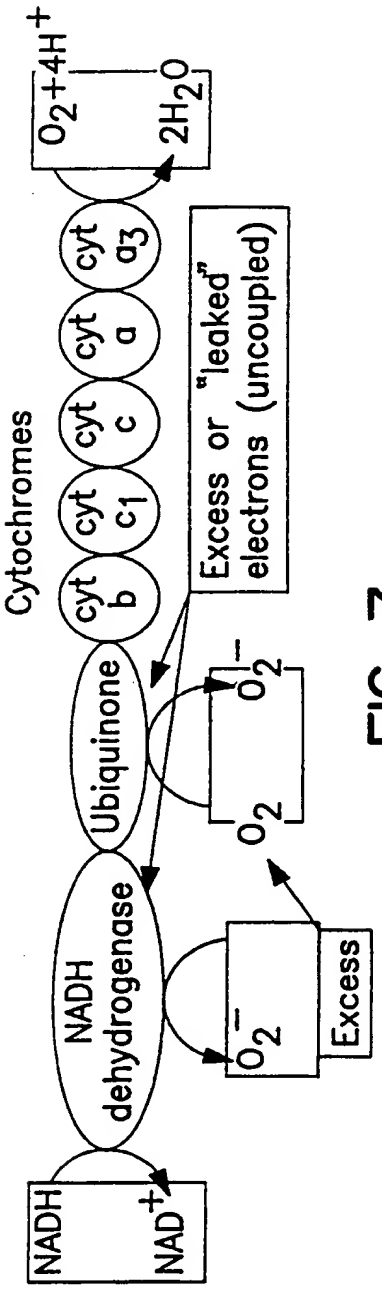

$O_2+4H^+$
$2H_2O$
Cytochromes
cyt a3
cyt a
cyt c
cyt c1
cyt b
Excess or "leaked" electrons (uncoupled)
Ubiquinone
$O_2^-$
$O_2$
NADH dehydrogenase
$O_2^-$
Excess
NADH
$NAD^+$

FIG. 7

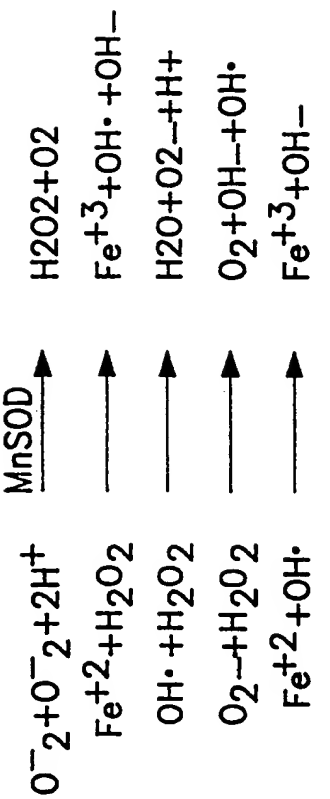

$O^-_2+O^-_2+2H^+$
MnSOD
$H_2O_2+O_2$
$Fe^{+2}+H_2O_2$
$Fe^{+3}+OH^\bullet+OH^-$
$OH^\bullet+H_2O_2$
$H_2O+O_2^-+H^+$
$O_2^-+H_2O_2$
$O_2+OH^-+OH^\bullet$
$Fe^{+2}+OH^\bullet$
$Fe^{+3}+OH^-$

FIG. 7a

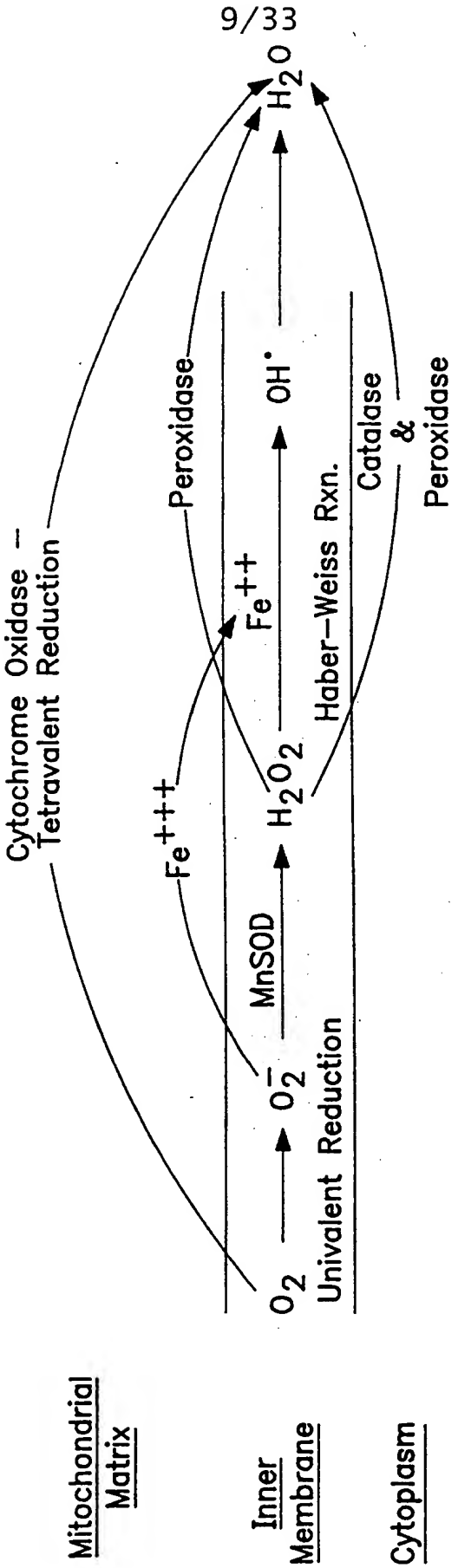

Cytochrome Oxidase –
Tetravalent Reduction
Peroxidase
Catalase
&
Peroxidase
$H_2O$
$Fe^{+++}$
$Fe^{++}$
$OH^{\bullet}$
$H_2O_2$
Haber–Weiss Rxn.
MnSOD
$O_2^-$
$O_2$
Univalent Reduction
Mitochondrial Matrix
Inner Membrane
Cytoplasm

FIG. 7b

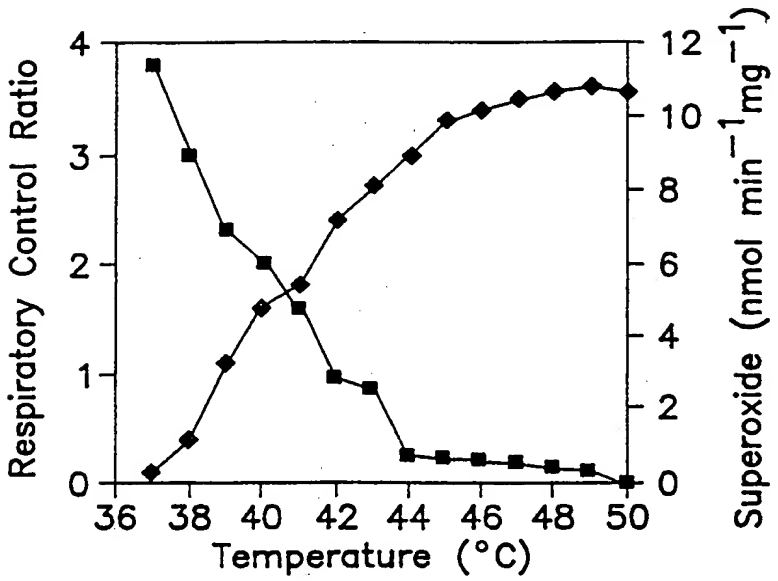

Respiratory Control Ratio
Superoxide (nmol min$^{-1}$mg$^{-1}$)
Temperature (°C)
0
1
2
3
4
0
2
4
6
8
10
12
36
38
40
42
44
46
48
50

FIG. 8a

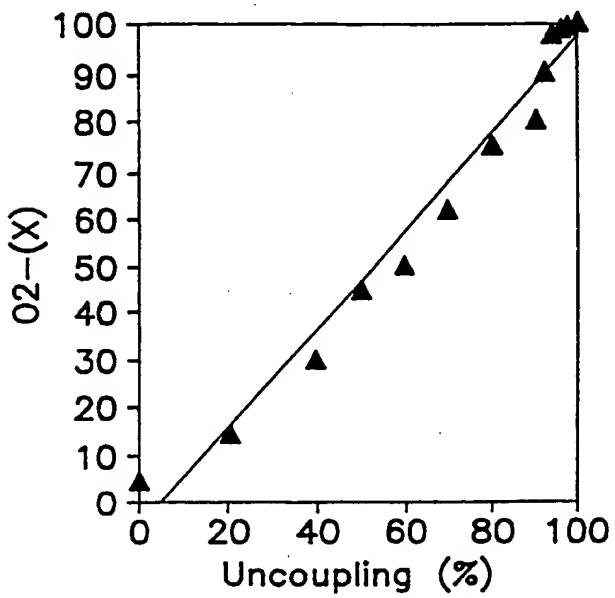

02-(X)
Uncoupling (%)
0
10
20
30
40
50
60
70
80
90
100
0
20
40
60
80
100

FIG. 8b

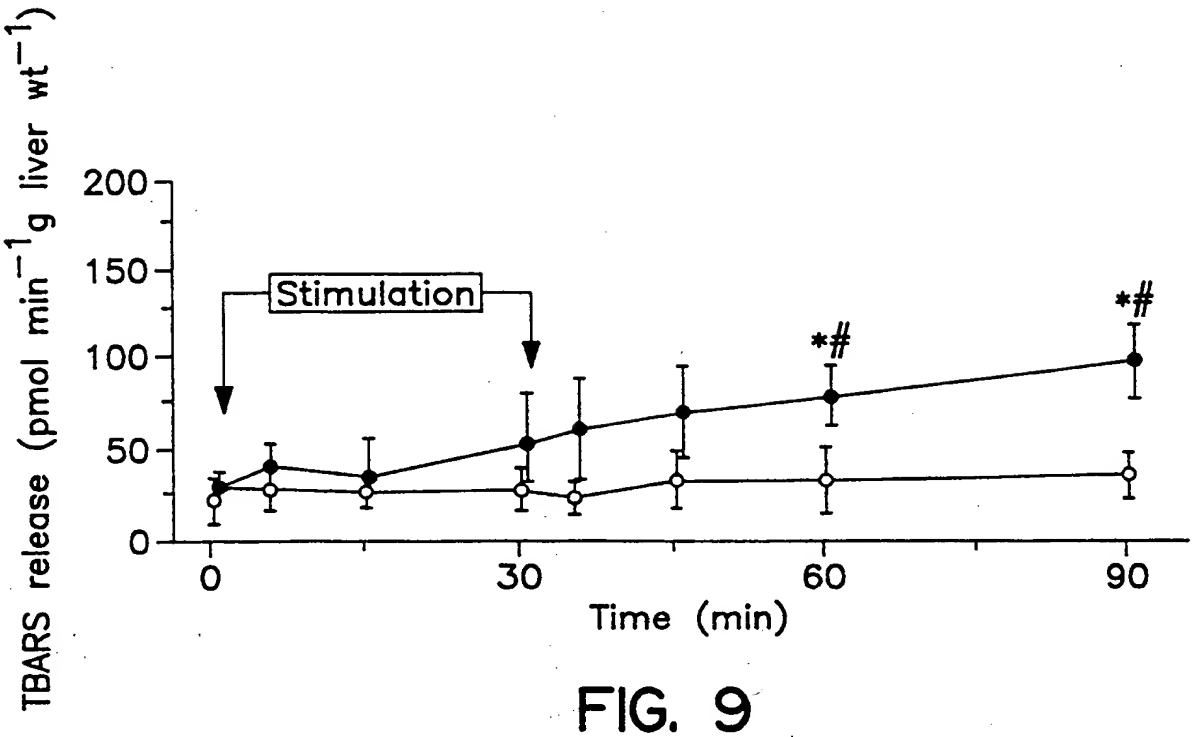

TBARS release (pmol min$^{-1}$g liver wt$^{-1}$)
200
150
100
50
0
Stimulation
*#
*#
0
30
60
90
Time (min)

FIG. 9

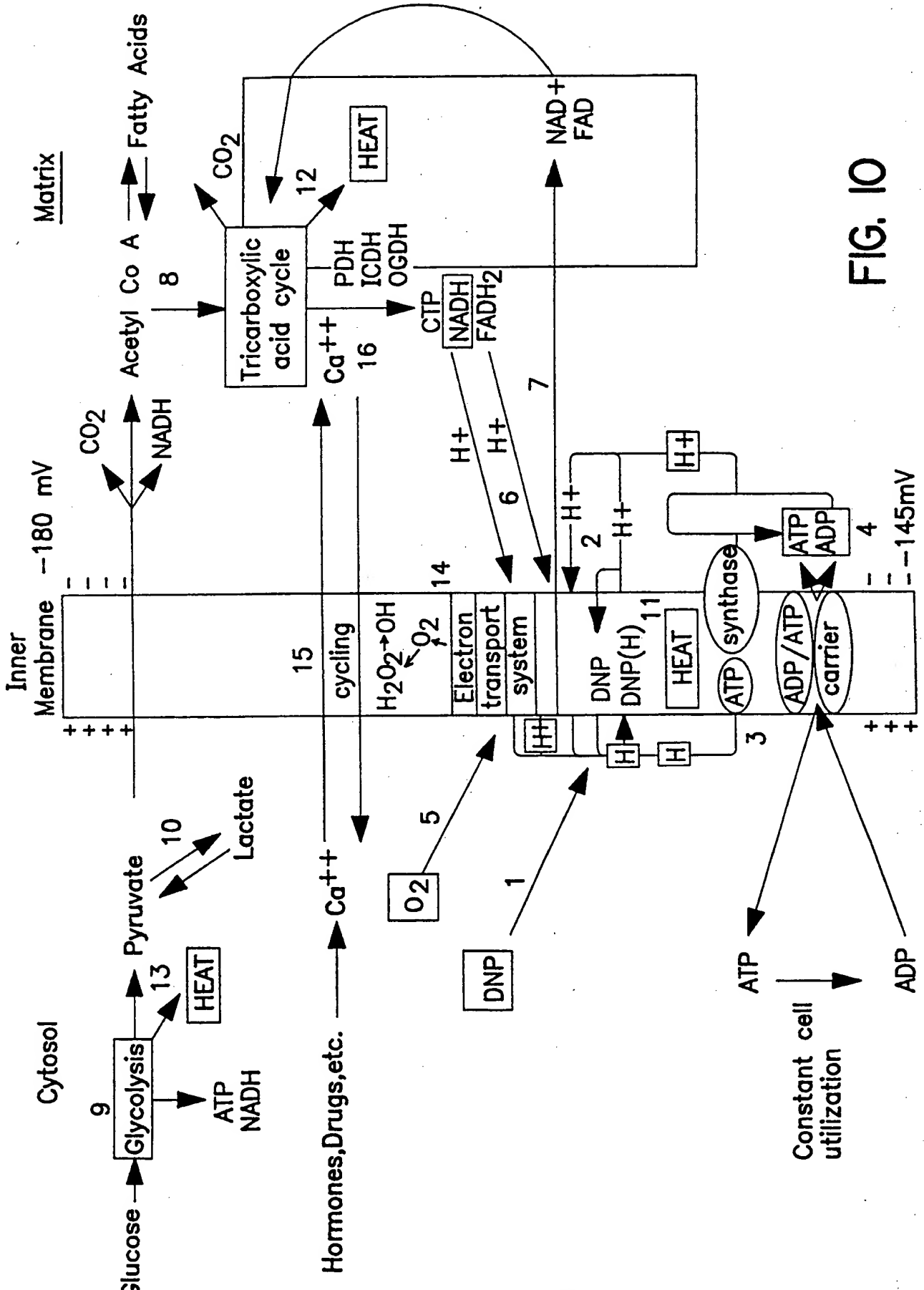

Matrix
Fatty Acids
Acetyl Co A
8
Tricarboxylic acid cycle
PDH
ICDH
OGDH
CTP
NADH
FADH2
Ca++
16
CO2
12
HEAT
NAD+
FAD
7
6
H+
2
4
ATP
ADP
synthase
ATP
ADP/ATP carrier
−180 mV
−145mV
Inner Membrane
14
15
cycling
H2O2→OH
O2
Electron transport system
DNP
DNP(H)
11
HEAT
3
5
O2
1
DNP
Cytosol
Pyruvate
10
Lactate
9
Glycolysis
13
HEAT
ATP
NADH
Glucose
Hormones,Drugs,etc.
Ca++
ATP
ADP
Constant cell utilization

FIG. 10

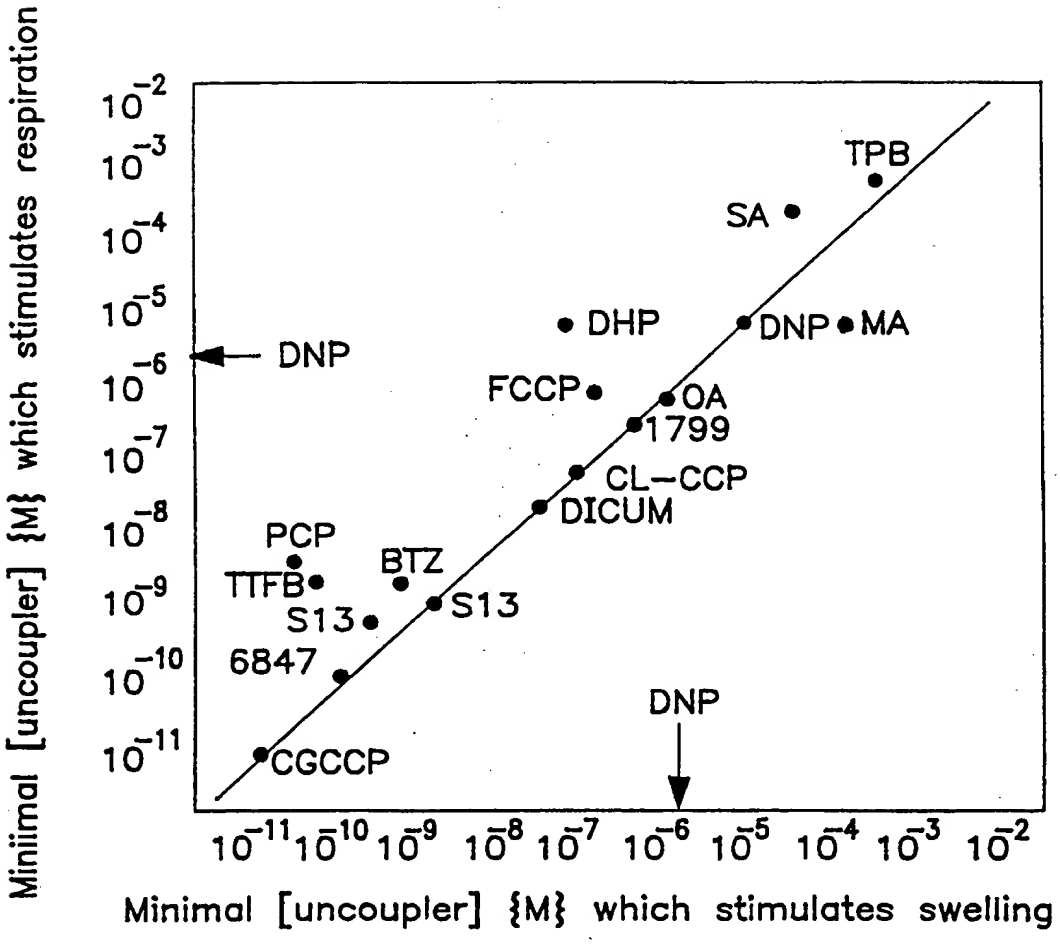

Miniimal [uncoupler] {M} which stimulates respiration
$10^{-2}$
$10^{-3}$
$10^{-4}$
$10^{-5}$
$10^{-6}$
$10^{-7}$
$10^{-8}$
$10^{-9}$
$10^{-10}$
$10^{-11}$
TPB
SA
DHP
DNP
MA
DNP
FCCP
OA
1799
CL–CCP
DICUM
PCP
BTZ
TTFB
S13
S13
6847
DNP
CGCCP
$10^{-11}$ $10^{-10}$ $10^{-9}$ $10^{-8}$ $10^{-7}$ $10^{-6}$ $10^{-5}$ $10^{-4}$ $10^{-3}$ $10^{-2}$
Minimal [uncoupler] {M} which stimulates swelling

FIG. 11

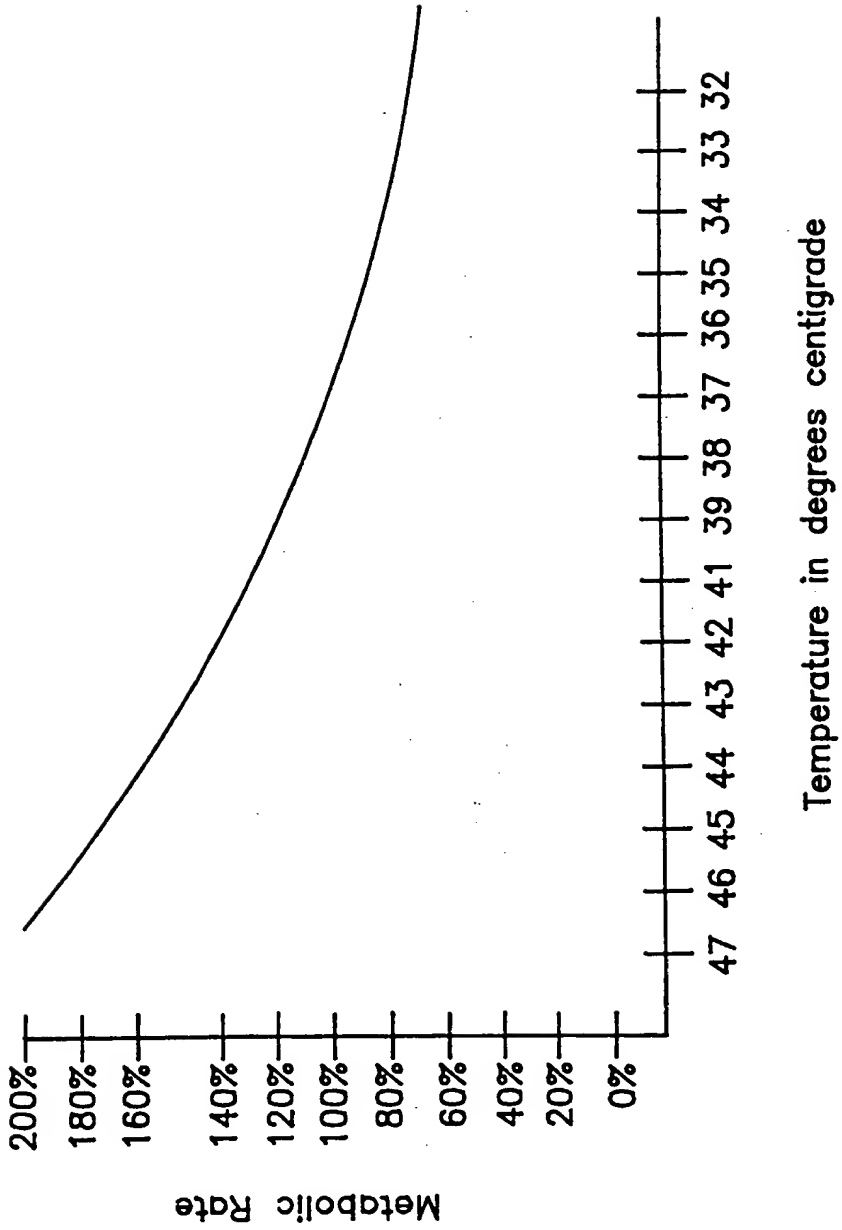

Metabolic Rate
200%
180%
160%
140%
120%
100%
80%
60%
40%
20%
0%
47 46 45 44 43 42 41 39 38 37 36 35 34 33 32
Temperature in degrees centigrade

FIG. IIa

| Tissue | Mass (kg)* | Blood Flow (L/min)* | Metabolic Rate (W)* |
|---|---|---|---|
| Liver | 2.6 | 1.5 | 18 |
| Brain | 1.4 | 0.75 | 17 |
| Skeletal Muscle | 31.0 | 1.2 to 24 | 17 to 350 |
| Heart Muscle | 0.3 | 0.25 to 31 | 10 to 31 |
| Kidney | 0.3 | 1.25 | 6 |
| Skin | 3.6 | 0.4 to 2.8 | 4 to 30 |

* Mean values under physiologic conditions.

FIG. 12

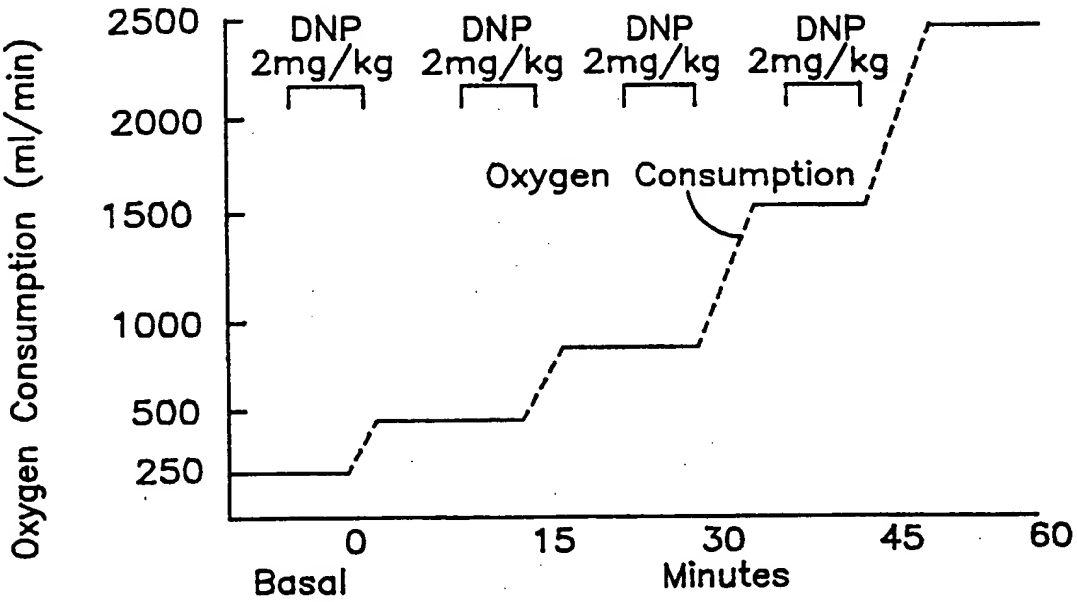

2500
2000
1500
1000
500
250
Oxygen Consumption (ml/min)
DNP 2mg/kg
DNP 2mg/kg
DNP 2mg/kg
DNP 2mg/kg
Oxygen Consumption
0
Basal
15
30
45
60
Minutes

FIG. 13

| | Patient Name: Sex:F | Wt: 68 kg | Ht: 165cm | BP 130/80 | Resp:20 | | | |
|---|---|---|---|---|---|---|---|---|
| TIME (min) | MEDICATION/PROCEDURE (type/dose/route) | *VO2 (ml/min) | *HEAT (Kcal/hr) | *TEMP (C) | *HR (BPM) | *VCO2 (ml/min) | *VE (L/min) | NOTES |
| (-5 to 0) | Body Wet Suit | 240 | 70.2 | 37.1 | 88 | 210 | 7.1 | Base mean over 5 minutes |
| 0 to 2 | *DNP-1mg/kg/IV | | | | | | | DNP infused over 2 minutes |
| 10 | | 260 | 75.8 | 37.4 | 86 | 300 | 7.6 | All vital signs normal |
| 20 | DNP-2mg/kg/IV | 340 | 99.1 | 37.2 | 86 | 398 | 8.8 | DNP infused over 2 minutes |
| 40 | DNP-2mg/kg/IV | 600 | 175 | 37.3 | 82 | 490 | 16.9 | DNP infused over 2 minutes |
| 60 | | 710 | 207 | 39.1 | 94 | 690 | 18 | |
| 90 | | 780 | 227 | 39.8 | 90 | 710 | 16.2 | |
| 120 | | 760 | 221 | 40.2 | 92 | 680 | 17.1 | |
| 150 | Body Wet Suit Removed | 700 | 204.2 | 40.3 | 98 | 680 | 18.1 | |
| 160 | | 680 | 198 | 40.1 | 105 | 670 | 16.9 | Evaporative heat loss initiated |
| 240 | | 600 | 175 | 39.2 | 98 | 590 | 14.2 | |
| 300 | | 500 | 145 | 38.4 | 96 | 490 | 14 | |
| 360 | Final Reading | 340 | 99.1 | 37.6 | 88 | 300 | 11.4 | Vital signs stable |
| | | | | | | | | |
| | *DNP=2,4-dinitrophenol | | | | | | | |
| | *VO2=oxygen consumption | | | | | | | |
| | *Heat=VO2 x 4.862 Kcal* | | | | | | | |
| | *Temp = degrees centigrade | | | | | | | |
| | *HR = heart rate (beats/min) | | | | | | | |
| | *VCO2=carbon dioxide produced | | | | | | | |
| | *VE=expired air volume (liters/min) | | | | | | | |
| | | | | | | | | |
| | NOTE: 1 liter of oxygen consumed yields 4.862 kilocalories of heat at standard conditions | | | | | | | |

FIG. 14

| | Patient Name: Sex:M | Wt: 90kg | Ht: 177.8cm | BP 140/80 | Resp:18 | | | |
|---|---|---|---|---|---|---|---|---|
| TIME | MEDICATION/PROCEDURE | VO2 | HEAT | TEMP | HR | VCO2 | VE | NOTES |
| (min) | (type/dose/route) | (ml/min) | (Kcal/hr) | (C) | (BPM) | (ml/min) | (L/min) | |
| -60 | diazepam, 10mg/PO | | | | | | | Dressed in modified wet suit |
| -15 | IV fluids, D5W/.5NS+7meq K+ | | | | | | | Drip rate @ 12cc/kg/hr |
| | placement of monitors | | | | | | | |
| (-10 to 0) | baseline readings | 300 | 87.5 | 37 | 76 | 180 | 6.5 | mean recordings over 10 minutes |
| 0 to 3 | DNP, 1mg/kg/IV | 380 | 110 | 37.1 | 78 | 220 | 8.1 | DNP infused over 2 min period |
| 10 | | 410 | 119 | 37.3 | 76 | 380 | 12.4 | complained of some IV "burning" |
| 20 | DNP, 3mg/kg/IV | 420 | 123 | 37 | 82 | 330 | 11.8 | DNP infused over 2 min period |
| 40 | | 620 | 180 | 37.2 | 84 | 680 | 17.8 | stable 5 min post injection |
| 40 to 42 | Glucagon, 0.5mg/kg/Ivdrip/hr | 760 | 221 | 37.5 | 86 | 750 | 18.2 | readings stabilized at 15 minutes |
| 50 | | 800 | 236 | 37.8 | 90 | 790 | 18.9 | |
| 60 to 70 | Glucagon, 1.0mg/kg/Ivdrip/hr | 810 | 250 | 38 | 94 | 840 | 21 | |
| 75 to 80 | Glucagon 2.0mg/kg/Ivdrip/hr | 860 | 260 | 38.5 | 100 | 890 | 21.7 | complaints of mild nausea |
| 90 | | 910 | 265 | 39.1 | 110 | 920 | 26.2 | no complaints |
| 100 | | 880 | 256 | 39.6 | 112 | 970 | 26.1 | states skin is "very warm" |
| 110 | | 960 | 279 | 39.9 | 110 | 940 | 24.3 | |
| 120 | | 880 | 256 | 40.1 | 112 | 980 | 25.2 | |
| 130 | | 900 | 262 | 40.3 | 115 | 850 | 26.5 | |
| 140 | | 890 | 260 | 40.1 | 112 | 1,050 | 27.8 | lower extremity uncovered |
| 150 | | 880 | 256 | 40.2 | 100 | 950 | 25.8 | wet suit opened |
| 160 | Glucagon discontinued | 830 | 242 | 40.1 | 110 | 900 | 26.7 | Total dose: glucagon=3mg |
| 170 | IVs discontinued, monitors removed | 810 | 236 | 39.5 | 100 | 880 | 24.5 | |
| 420 | Oral tube for VO2 | 360 | 105 | 37.2 | 88 | 400 | 8.1 | All vital signs normal |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

FIG. 15

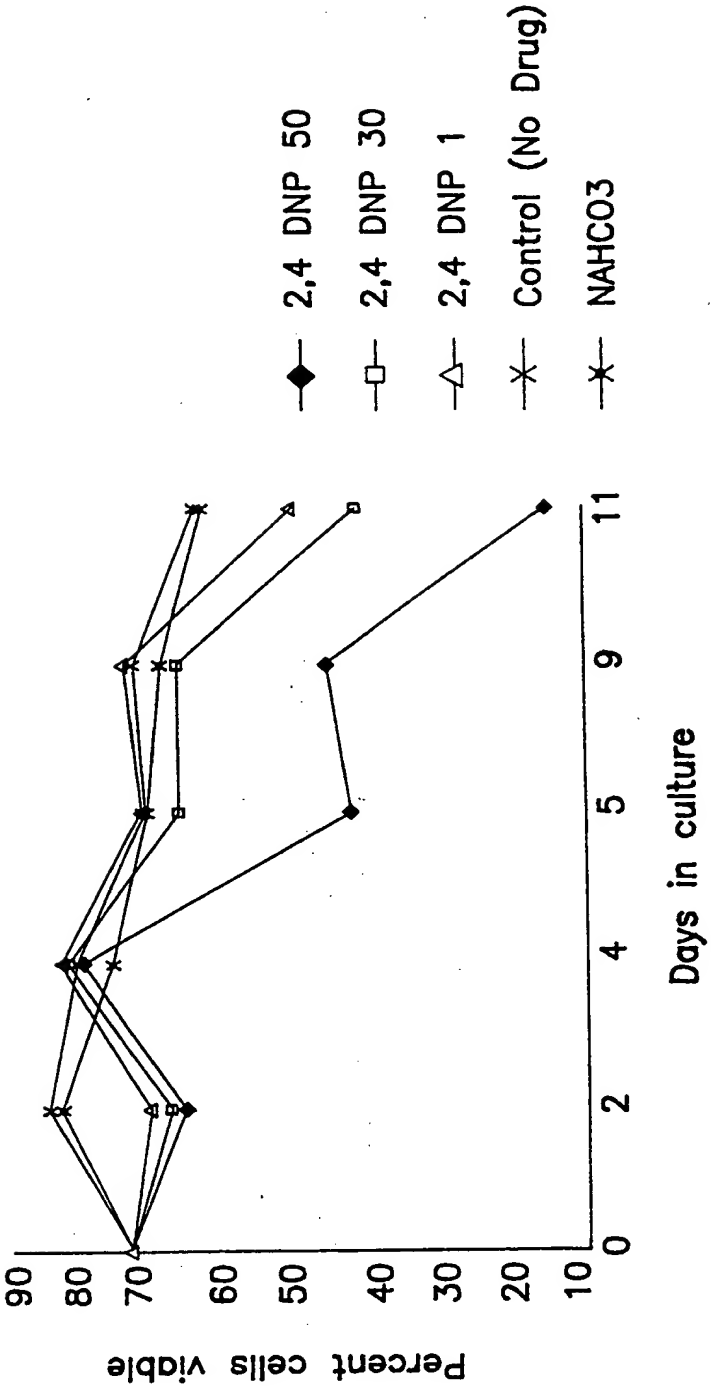

2,4 DNP 50
2,4 DNP 30
2,4 DNP 1
Control (No Drug)
NAHCO3
Percent cells viable
90
80
70
60
50
40
30
20
10
0
2
4
5
9
11
Days in culture

FIG. 16

| | Patient Name: Sex:M | Wt:60kg | Ht: 155cm | BP128/72 | Resp:20 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| TIME | MEDICATION/PROCEDURE | VO2 | HEAT | TEMP | HR | VCO2 | VE | NOTES |
| (min) | (type/dose/route) | (ml/min) | (Kcal/hr) | (C) | (BPM) | (ml/min) | (L/min) | |
| | dressed in cold water dry suit | | | | | | | |
| (-5 to 0) | Baseline | 300 | 87.5 | 38.1 | 85 | 275 | 5.9 | oral breathing tube used/room air |
| 0 to 2 | DNP, 2mg/kg/IV | 320 | 99 | 38.2 | 86 | 290 | 6.2 | DNP infused over a 2 min period |
| 20 | | 340 | 99.1 | 38.1 | 88 | 300 | 8.1 | |
| 30 | | 380 | 110 | 38.6 | 92 | 350 | 9.6 | |
| 40 to 42 | DNP, 2mg/kg/IV | 340 | 99 | 38.8 | 90 | 360 | 10 | DNP infused over a 2 min period |
| 60 | | 610 | 178 | 39.4 | 90 | 390 | 11.4 | BP: falls to 110/50 |
| 90 | | 630 | 183 | 39.5 | 92 | 610 | 15.2 | BP: 105/60 |
| 92 | Levophed, 1ugm/min/Ivdrip | 650 | 189.5 | 39.5 | 92 | 630 | 21 | BP: 100/60 |
| 96 | | 790 | 230 | 39.8 | 102 | 770 | 17.4 | BP: 110/60 |
| 100 | | 850 | 247 | 40.1 | 115 | 830 | 16.7 | BP: 130/80 |
| 115 | Levophed decreased to 0.5ugm/min | 1,000 | 291 | 41.5 | 110 | 1,200 | 25.8 | Stable BP @ 130/80 |
| 125 | | 980 | 285 | 41.6 | 108 | 1,040 | 26.6 | Rt. Lower extremity uncovered |
| 160 | | 880 | 256 | 41.1 | 110 | 990 | 27.2 | |
| 180 | | 960 | 279 | 41.5 | 112 | 1,000 | 29.8 | |
| 220 | | 1,000 | 291 | 41.3 | 110 | 1,100 | 28.3 | |
| 230 | | 800 | 233 | 41.1 | 105 | 920 | 27.8 | VO2 falling |
| 240 | | 760 | 221 | 41.3 | 108 | 830 | 21.1 | VO2 continues to fall |
| 242 to 244 | DNP, 1mg/kg/IV | 890 | 260 | 41.4 | 110 | 980 | 24.8 | DNP infused over a 2 min period |
| 280 | | 1,080 | 315 | 41.6 | 115 | 1,280 | 28.6 | Both lower extremities uncovered |
| 300 | | 1,000 | 291 | 41.3 | 110 | 1190 | 29.5 | |
| 320 | Levophed stopped | 1,100 | 320 | 41.1 | 108 | 1240 | 31.1 | |
| 360 | | 950 | 277 | 40.9 | 98 | 1,040 | 29.2 | cold water dry suit |
| 390 | | 910 | 265 | 39.2 | 94 | 990 | 28.5 | |
| 420 | Monitors removed | 830 | 242 | 38.6 | 92 | 920 | 16.8 | |
| 450 | oral breathing tube | 420 | 123 | 37.8 | 88 | 510 | 10.2 | |
| 480 | | 340 | 99.1 | 37.5 | 90 | 440 | 8.9 | Vital signs within normal limits |

FIG. 17

| | Patient Name: Sex:F | Wt:60kg | Ht: 160cm | BP130/70 | Resp:20 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| TIME | MEDICATION/PROCEDURE | VO2 | HEAT | TEMP | HR | VCO2 | VE | NOTES |
| (min) | (type/dose/route) | (ml/min) | (Kcal/hr) | (C) | (BPM) | (ml/min) | (L/min) | |
| | | | | | | | | |
| (-240) | alprazolam, 2mg/PO | | | | | | | to calm anxiety |
| (-20) | dressed in dry water immersion suit | | | | | | | dressed |
| (-15) | IV fluids, D5W1/2NS+7meg K+ | | | | | | | Monitors & Foley attached |
| (-10 to 0) | Baseline Readings | 220 | 64.2 | 37.3 | 86 | 190 | 5.2 | |
| 0 to 2 | DNP, 1mg/kg/IV | 230 | 67 | 37.3 | 90 | 200 | 5.5 | DNP infused over a 2min period |
| 20 | | 250 | 72.9 | 37.2 | 88 | 230 | 6.3 | |
| 20 to 22 | DNP, 2mg/kg/IV | 250 | 72.9 | 37.8 | 86 | 220 | 6.3 | DNP infused over a 2min period |
| 30 | DNP, 1mg/kg/IV | 310 | 90.4 | 38.4 | 86 | 290 | 10.4 | |
| 50 | | 380 | 110 | 38.9 | 90 | 350 | 14 | |
| 50 to 54 | DNP, 1.0mg/kg/IV | 400 | 116 | 39.5 | 90 | 390 | 14 | DNP infused over a 2min period |
| 70 | | 600 | 175 | 40.2 | 110 | 590 | 18 | Patient became briefly agitated |
| 80 | | 570 | 166 | 40.8 | 98 | 550 | 18 | |
| 90 | | 500 | 145 | 40.1 | 100 | 510 | 15 | 20 sec readings show fall in VO2 |
| 95 to 98 | Dopamine Drip/3mcg/kg/min | 520 | 151.6 | 40.2 | 115 | 500 | 15.8 | |
| 100 | | 630 | 183 | 40.3 | 115 | 610 | 18 | |
| 110 | | 680 | 198.2 | 40.2 | 110 | 690 | 20 | |
| 150 | | 710 | 207 | 40.5 | 110 | 700 | 21 | |
| 180 | | 680 | 198.2 | 40.6 | 115 | 690 | 19 | Dopamine discontinued |
| 250 | | 650 | 189 | 40.1 | 110 | 660 | 19 | |
| 255 | Insulating Suit open | 600 | 175 | 39.6 | 112 | 610 | 22 | patient complains of fatigue |
| 280 | | 430 | 125 | 39.1 | 115 | 410 | 14 | |
| 320 | | 340 | 99.1 | 37.8 | 92 | 330 | 12 | |
| 400 | chills & rigors | | | | | | | |
| 401 to 405 | IV fluids, dopamine 2mcg/kg/min | 380 | 110 | 38.7 | 100 | 270 | 15 | IV fluids & observation |
| 500 to 610 | Symptoms subside | 250 | 72.8 | 37.8 | 90 | 230 | 7 | Jarisch-Herxheimer? |
| | | | | | | | | |

FIG. 18

| | Patient Name: Sex:F | Wt:55kg | Ht: 154cm | BP100/50 | Resp:22 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| TIME | MEDICATION/PROCEDURE | VO2 | HEAT | TEMP | HR | VCO2 | VE | NOTES |
| (min) | (type/dose/route) | (ml/min) | (Kcal/hr) | (C) | (BPM) | (ml/min) | (L/min) | |
| | | | | | | | | |
| (-50 to-40) | covered in water soaked blanket | | | | | | | |
| (-40 to-30) | polyethylene wrap around blanket | | | | | | | 3 units packed RBC-24 hr prior |
| (-30 to-10) | Carboplatin-45mg/mitomycin-24mg | | | | | | | IV fluids, D5W1/2NS+10meq K+ |
| | (total dose given by IV infusion) | | | | | | | |
| (-10 to 0) | | 230 | 67 | 37.6 | 90 | 200 | 5.9 | Mean values over 10 min period |
| 0 to 1 | mephenteramine sulfate/30mg/IM | 250 | 72.9 | 37.7 | 85 | 220 | 6.3 | |
| 10 | | 320 | 93.3 | 37.9 | 96 | 290 | 5.9 | BP increased to 140/88 |
| 15 | | 340 | 99.1 | 38.1 | 98 | 300 | 7.5 | BP stable at 140/90 |
| 20 to 22 | DNP, 1.0mg/kg/IV | 380 | 110 | 38.2 | 100 | 350 | 6.6 | DNP infused over a 2 min period |
| 23 | | 450 | 131.2 | 38.2 | 105 | 440 | 9.8 | |
| 28 | | 400 | 116.6 | 38.8 | 105 | 510 | 12.9 | |
| 30 | | 430 | 125.4 | 39 | 110 | 500 | 13.2 | |
| 40 to 42 | DNP, 0.5mg/kg/IV | 480 | 139.9 | 39.4 | 110 | 560 | 15.8 | DNP infused over a 2 min period |
| 50 | | 520 | 151.6 | 39.9 | 115 | 540 | 16.2 | |
| 60 | DNP, 0.5mg/kg/IV | 640 | 186.6 | 40.3 | 112 | 660 | 18.4 | DNP infused over a 2 min period |
| 70 | | 660 | 192.4 | 40.8 | 115 | 720 | 21.3 | |
| 80 | DNP, 0.5mg/kg/IV | 780 | 227.4 | 40.9 | 110 | 880 | 19.3 | DNP infused over a 2 min period |
| 90 | | 800 | 233 | 41.2 | 120 | 850 | 18.7 | |
| 100 | | 820 | 239 | 41.4 | 125 | 810 | 20.6 | |
| 120 | | 790 | 230.4 | 41.5 | 115 | 740 | 15.5 | |
| 130 | | 800 | 233 | 41.4 | 110 | 850 | 14.9 | |
| 131 to 133 | DNP, 0.5mg/kg/IV | 820 | 239 | 41.4 | 115 | 790 | 15.8 | DNP infused over a 2 min period |
| 150 | | 810 | 236 | 41.4 | 112 | 840 | 13.7 | |
| 160 | | 800 | 233 | 41.4 | 120 | 690 | 14.1 | |
| 170 | | 850 | 247 | 41.2 | 115 | 870 | 16.7 | |
| 180 | Doxifluridine, 600mg/PO | 820 | 239 | 41.3 | 110 | 890 | 13.7 | |
| 200 | | 820 | 239 | 41.4 | 115 | 850 | 15.3 | |
| 210 | | 790 | 230.4 | 41.2 | 102 | 770 | 17.4 | IV fluids discontinued |
| 240 | | 630 | 183 | 38.6 | 100 | 550 | 14.3 | |
| 260 | | 420 | 123 | 37.5 | 102 | 395 | 10.8 | Monitors removed |

FIG. 19





WO 00/06143
PCT/US99/16940
09/744622

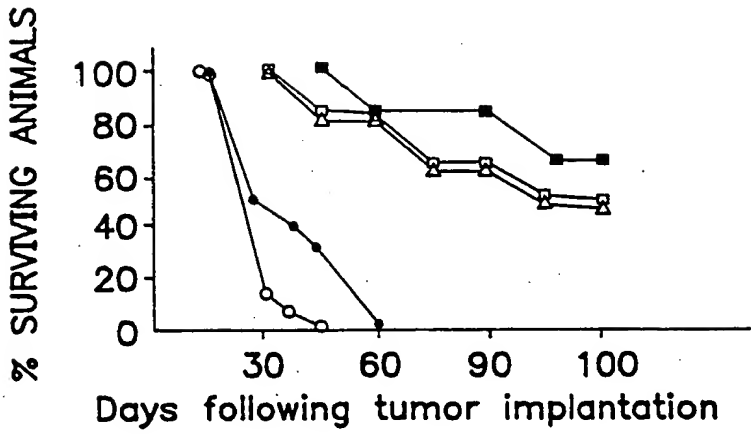

% SURVIVING ANIMALS
100
80
60
40
20
0
30
60
90
100
Days following tumor implantation

FIG. 20

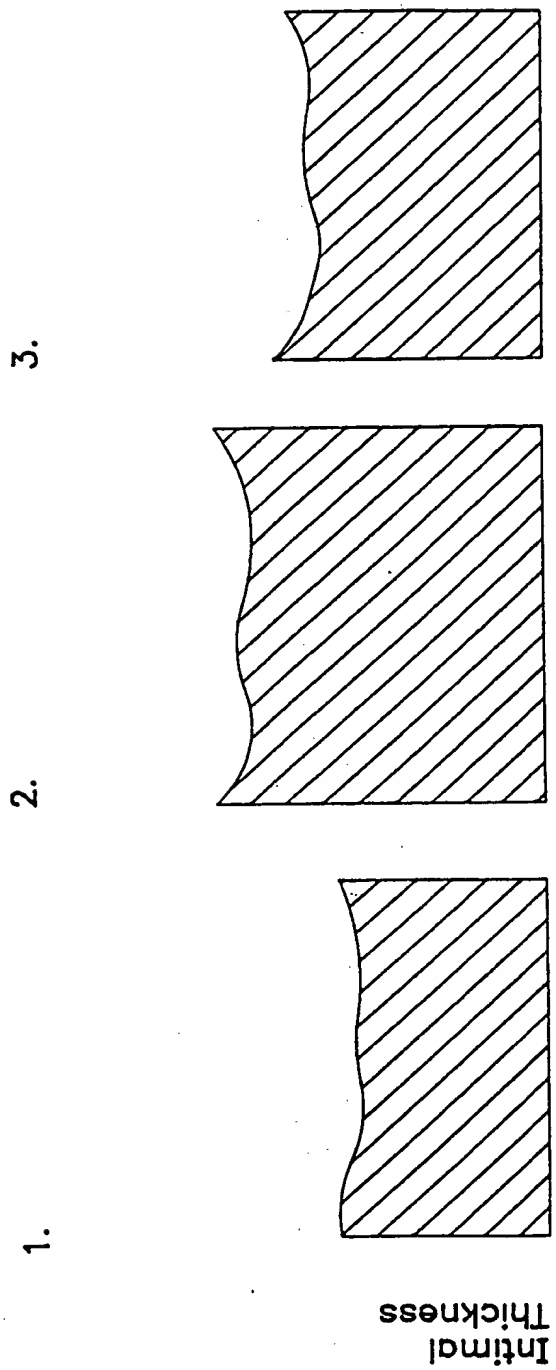



FIG. 21

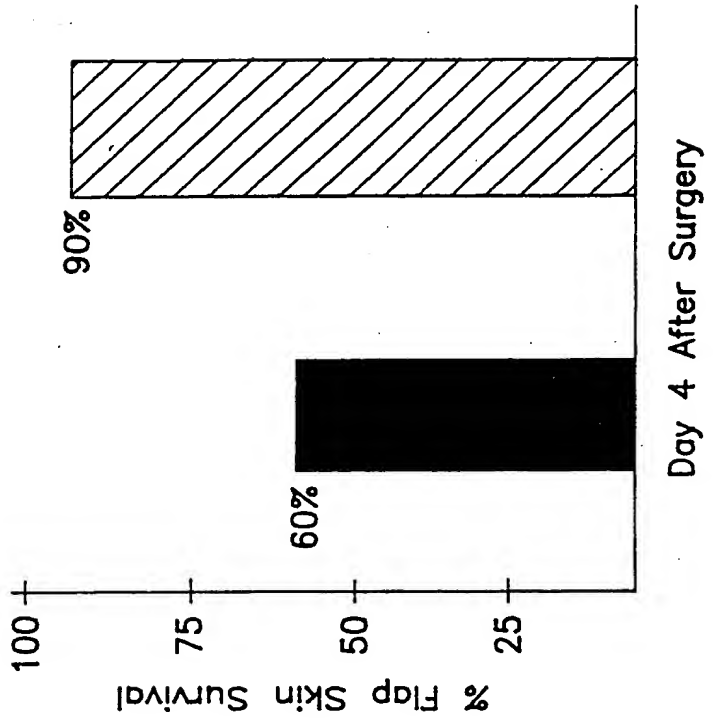

% Flap Skin Survival
100
75
50
25
90%
60%
Day 4 After Surgery

FIG. 23

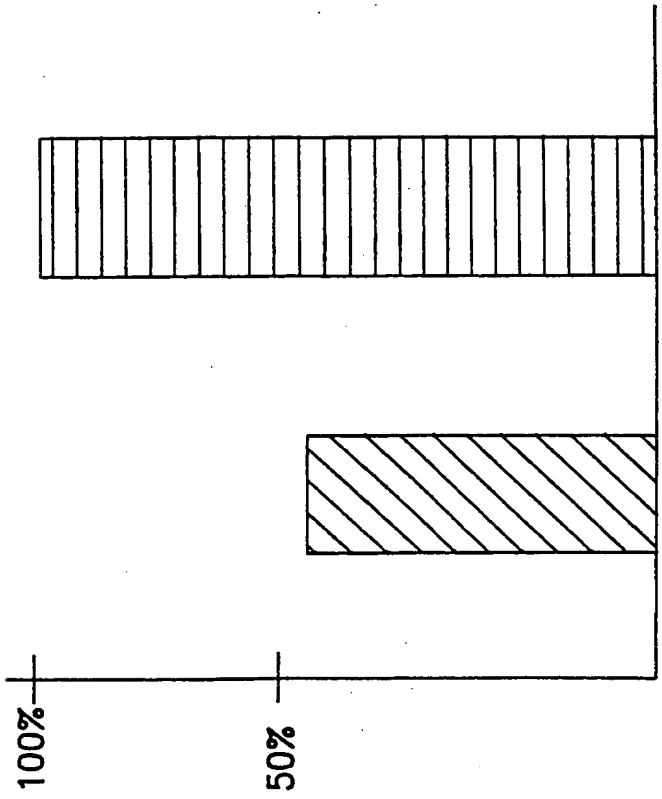

Percent Survival
100%
50%

FIG. 22

| | Patient Name: Sex:M | Wt:65kg | Ht: 175cm | BP135/80 | Resp: 18 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | MEDICATION/PROCEDURE | VO2 | HEAT | TEMP | HR | VCO2 | VE | NOTES | |
| (min) | (type/dose/route) | (ml/min) | (Kcal/hr) | (C) | (BPM) | (ml/min) | (L/min) | | |
| | Phenytoin, 200mg/TID/PO | | | | | | | Increased for 3 days | |
| (-10 TO 0) | Baseline Readings | 230 | 67 | 37.5 | 86 | 210 | 4.9 | | |
| 0 | DNP, 300mg/PO | 220 | 64 | 37.5 | 84 | 200 | 5.1 | DNP by mouth with H2O | |
| 20 | | 230 | 67 | 37.4 | 88 | 210 | 5 | | |
| 60 | | 250 | 73 | 37.3 | 88 | 220 | 5.5 | | |
| 120 | | 300 | 87 | 37.5 | 82 | 280 | 6.3 | | |
| 140 | FDG/Bolus/IV | | | | | | | | |
| 180 | PET Scan initiated | 320 | 93 | 37.5 | 86 | 300 | 8 | | |
| 210 | PET Scan completed | 340 | 99 | 37.5 | 86 | 310 | 10 | No complaints | |
| 480 | | 260 | 76 | 37.4 | 84 | 250 | 7 | No complaints | |

FIG. 24

| | Patient Name: Sex:F | Wt:60kg | Ht: 164cm | BP120/72 | Resp:18 | | | |
|---|---|---|---|---|---|---|---|---|
| TIME | MEDICATION/PROCEDURE | VO2 | HEAT | TEMP | HR | VCO2 | VE | NOTES |
| (min) | (type/dose/route) | (ml/min) | (Kcal/hr) | (C) | (BPM) | (ml/min) | (L/min) | |
| (-10 to 0) | Baseline | 180 | 52 | 37.7 | 88 | 160 | 4.8 | |
| 1 to 2 | DNP/1mg/kg/IV | 180 | 52 | 37.6 | 86 | 165 | 4.6 | DNP infused over 2 min |
| 22 | | 210 | 61 | 37.7 | 86 | 190 | 4.8 | No complaints |
| 22 to 24 | DNP/2mg/kg/IV | 200 | | | 84 | 190 | 50 | DNP infused over 2 min |
| 60 | Thermal imaging | 300 | 93 | 37.2 | 84 | 300 | 5.8 | In isothermally controlled room |

FIG. 25

| | Patient Name: Sex:M | Wt:72kg | Ht: 175cm | BP140/86 | Resp:22 | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| TIME | MEDICATION/PROCEDURE | VO2 | HEAT | TEMP | HR | VCO2 | VE | NOTES |
| (min) | (type/dose/route) | (ml/min) | (Kcal/hr) | (C) | (BPM) | (ml/min) | (L/min) | |
| | | | | | | | | |
| | 2 units packed RBCs | | | 37.6 | 88 | | | 48 hours prior to treatment |
| (-240) | Lactated Ringers/IV | | | | | | | 100cc/hour |
| (-8 to 0) | Baseline studies | 250 | 73 | 37.6 | 88 | 220 | 6.4 | |
| | | | | | | | | |
| 0 to 2 | DNP, 1mg/kg/IV | 260 | 75.8 | 37.8 | 88 | 230 | 6.3 | |
| 20 | | 340 | 99 | 37.9 | 92 | 330 | 12 | |
| 30 | | 360 | 105 | 37.9 | 90 | 320 | 11 | |
| 45 to 47 | DNP, 1mg/kg/IV | 340 | 99 | 37.9 | 94 | 340 | 12 | DNP infused over a 2min period |
| 60 | | 420 | 122 | 38 | 92 | 400 | 14 | |
| 70 | Methylene blue, 2mg/kg/IV | | | | | | | administered in 35ml-20min infusion |
| 80 | | 430 | 125 | 37.9 | 96 | 410 | 15 | |
| 90 | | 500 | 145 | 38 | 96 | 490 | 16 | Patient feels "warm" |
| 110 | | 480 | 140 | 38.1 | 94 | 460 | 18 | |
| 130 | | 430 | 125 | 38.2 | 92 | 410 | 16 | |
| 150 | | 390 | 114 | 38.3 | 96 | 380 | 14 | |
| 180 | | 380 | 110 | 38.3 | 96 | 360 | 15 | |
| 200 | | 360 | 105 | 38.3 | 92 | 340 | 14 | |
| 200 to 202 | DNP, 1mg/kg/IV | 370 | 108 | 38.2 | 92 | 350 | 15 | DNP infused over a 2min period |
| 222 | | 450 | 131 | 38.4 | 92 | 430 | 16 | no complaints |
| 240 | | 490 | 143 | 38.5 | 94 | 470 | 15.7 | |
| 300 | | 520 | 151 | 38.8 | 96 | 490 | 16 | |
| 360 | Treatment terminated | 470 | 137 | 38.9 | 96 | 450 | 15.8 | |
| | | | | | | | | |
| 540 | | 380 | 110 | 38.4 | 92 | 350 | 14 | no complaints |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

FIG. 26





WO 00/06143
09/744622
PCT/US99/16940

| Treatment Period* | Serum PSA level* (ng/ml) | Acid Phosphatase (U/L) | Biopsy* | Clinical Findings |
|---|---|---|---|---|
| 0 | 58 | 1.2 | High grade adeno-carcinoma, Gleason grade 8 | Bone pain, lack of appetite, Karnofsky score of 6. |
| Day 6 | 68 | 1.6 | ——— | Decrease in bone pain |
| Day 8 | 125 | 1.6 | ——— | Increased appetite, decrease bone pain. |
| Day 14 | 88 | 1.4 | ——— | Off all pain meds. Marked increase in appetite. |
| 6 weeks | 30 | 1 | ——— | Karnofsky score of 7. Remains pain free |
| 10 weeks | 18 | 0.6 | over 95% tumor necrosis, rare intact acini; cyst-like structures. | Karnofsky score 8. Pain free |
| 12 weeks | 12 | 0.6 | ——— | Gained 8.2kg weight. Pain free |
| 4 months | 6.5 | 0.65 | Extensive fibrosis. Increase in stromal cells. Occasional tumor cells with reduced cytoplasm | Total of 9.3kg of weight gain. Pain free. Karnofsky score of 9 |

*Treatment period – DNP given IV every other day x 30, repeated after 2 weeks for additional 30 days; then, 250mg/orally/2 times daily for 5 days and, recycled after no DNP for 2 days for a total period of 4 months.

*PSA = Prostatic Specific Antigen

*Biopsy – Significant comments by pathologist .

FIG. 27

| | Patient Name: Sex:F | Wt:48kg | Ht: 150cm | BP128/82 | Resp:18 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIME | MEDICATION/PROCEDURE | VO2 | HEAT | TEMP | HR | VCO2 | VE | NOTES | |
| (min) | (type/dose/route) | (ml/min) | (Kcal/hr) | (C) | (BPM) | (ml/min) | (L/min) | | |
| (-360) | Interferon alpha/1.5million units/SQ | | | 37.5 | 76 | | | | |
| (-5 to 0) | Baseline readings | 160 | 47 | 37.5 | 76 | 140 | 3.5 | | |
| 0 to 2 | DNP, 1mg/kg/IV | 150 | 44 | 37.5 | 76 | 140 | 4 | DNP infused over 2min period | |
| 20 | | 210 | 61 | 37.7 | 80 | 190 | 4.2 | | |
| 20 to 22 | DNP, 1mg/kg/IV | | | | | | | DNP infused over 2min period | |
| 40 | | 250 | 73 | 38 | 84 | 220 | 5 | | |
| 50 to 52 | DNP, 2mg/kg/IV | | | | | | | DNP infused over 2min period | |
| 70 | | 360 | 105 | 38.3 | 86 | 330 | 9 | | |
| 170 to 172 | DNP, 2mg/kg/IV | 280 | 82 | 38.8 | 88 | 260 | 8.5 | DNP infused over 2min period | |
| 190 | | 420 | 122 | 38.8 | 88 | 400 | 12 | sweating profusely | |
| 240 | | 400 | 116 | 38.7 | 86 | 370 | 14 | very thirsty | |
| 300 | Treatment terminated | 380 | 110 | 38.7 | 90 | 350 | 14 | marked fatigue | |
| 420 | | 340 | 99 | 38.5 | 90 | 330 | 13 | no complaints other than severe fatigue | |

FIG. 28

| Treatment Period | HCV-RNA* (copies/ml) | AST* (IU/L) | ALT* (IU/L) |
|---|---|---|---|
| 0 | $5.8 \times 10^6$ | 78 | 85 |
| 48 hours | $4.6 \times 10^4$ | 400 | 610 |
| 14 days | non-detectable | 380 | 570 |
| 21 days | non-detectable | 100 | 78 |
| 18 months | non-detectable | 45 | 34 |

*HCV-RNA – Roche polymerase chain reaction methodology

*AST – aspartate aminotransferase

*ALT – alanine aminotransferase

FIG. 29

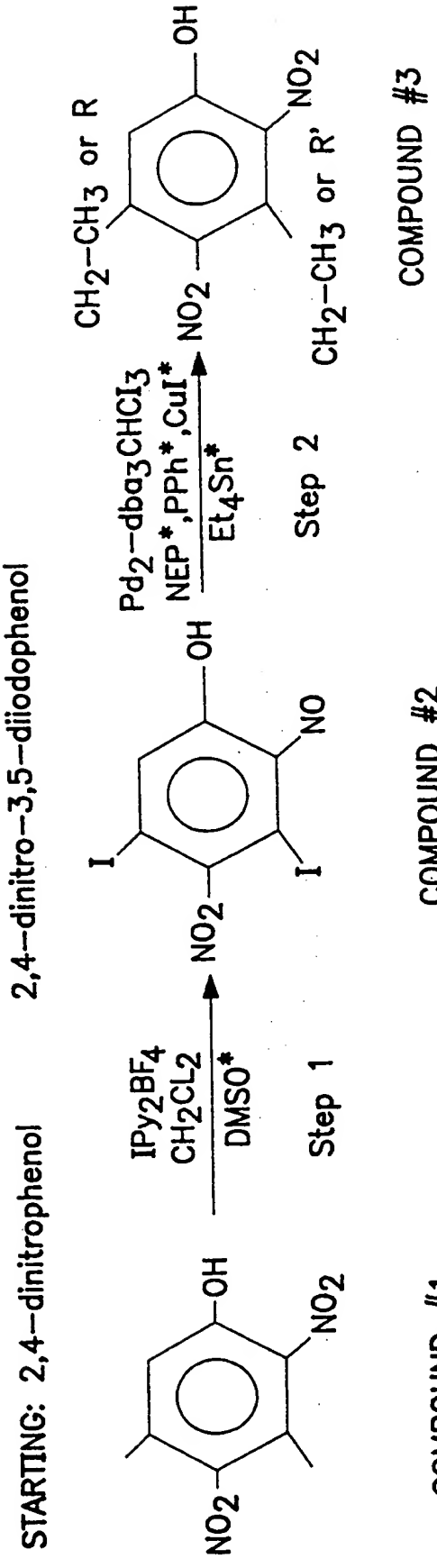
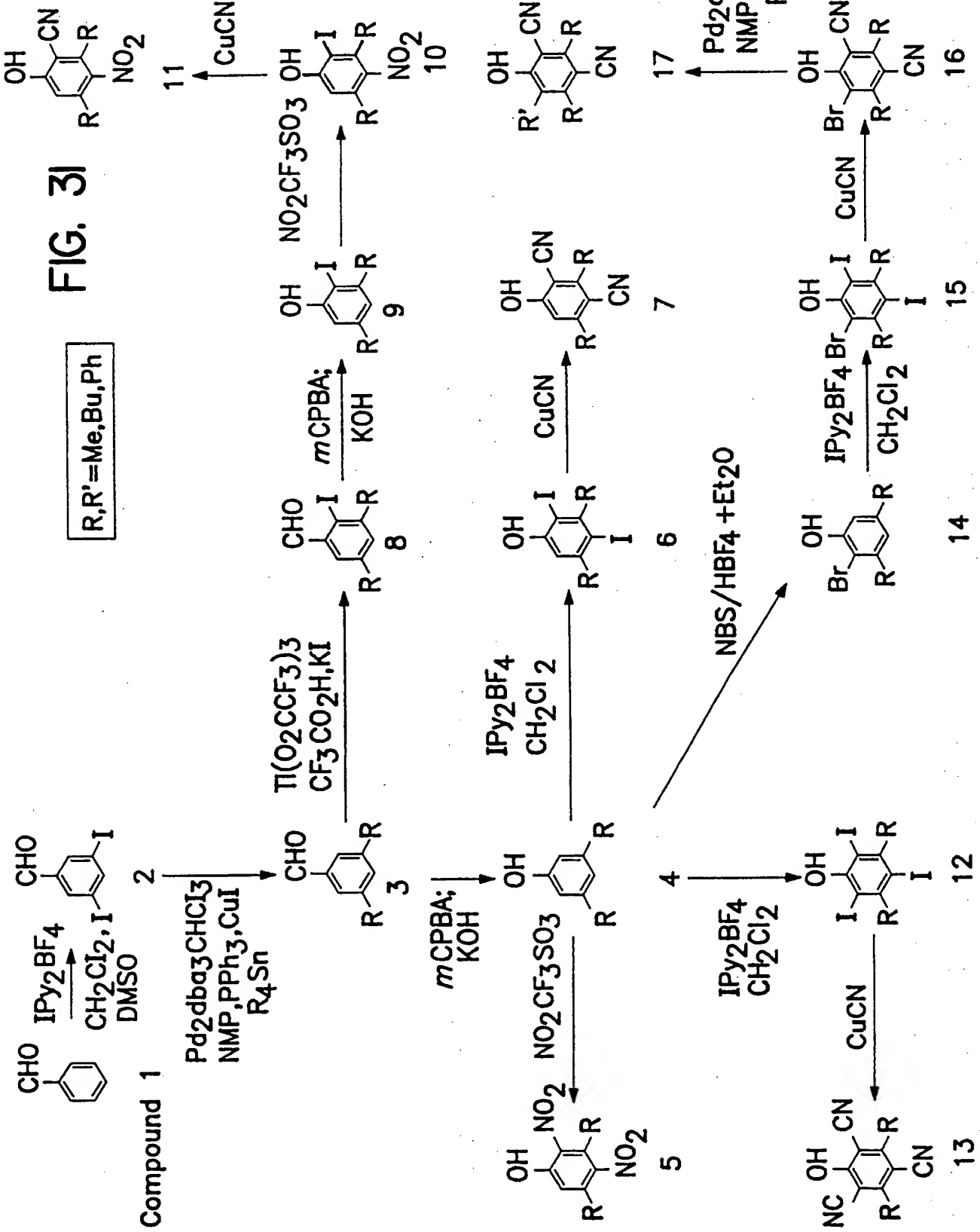

STARTING: 2,4-dinitrophenol
2,4-dinitro-3,5-diiodophenol
IPy2BF4
CH2CL2
DMSO*
Step 1
Pd2-dba3CHCl3
NEP*,PPh*,CuI*
Et4Sn*
Step 2
OH
NO2
I
NO
CH2-CH3 or R
CH2-CH3 or R'
COMPOUND #1
COMPOUND #2
COMPOUND #3

FIG. 30

FIG. 31


R,R'=Me,Bu,Ph
Compound 1
IPy2BF4
CH2Cl2, I
DMSO
Pd2dba3CHCl3
NMP,PPh3,CuI
R4Sn
Tl(O2CCF3)3
CF3CO2H,KI
mCPBA;
KOH
NO2CF3SO3
CuCN
IPy2BF4
CH2Cl2
NBS/HBF4+Et2O
Pd2dba3CHCl3
NMP,PPh3,CuI
R4Sn